July 30, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Docket Number: 2004N-0181

Dear Sir or Madam:

Thank you for the opportunity to review and respond to the document, *"Innovation or Stagnation? -- Challenge and Opportunity on the Critical Path to New Medical Products."* The Cystic Fibrosis Foundation is pleased that the Food and Drug Administration (FDA) has requested suggestions from its stakeholders on ways to speed the product development process for the 21st century. The drug development and approval process must be reformed to ensure that treatments will be brought to patients more quickly.

The Cystic Fibrosis Foundation is committed to developing treatments or a cure for cystic fibrosis (CF), a life-threatening genetic disease that affects the respiratory, digestive and reproductive systems of approximately 30,000 Americans. The median life expectancy for people with CF has now increased into the early thirties – an improvement over early childhood deaths common in the 1950s – but far from acceptable. The shortened life expectancy of people with CF creates an urgency for the development of new treatments in a much shorter time than the typical 14-year development timeline for most new drugs.

To meet the needs of people with CF, the CF Foundation aggressively pursues basic research and both the discovery and development of new treatments. The CF research strategy includes the use of cutting-edge research technologies, such as high-throughput screening, combinatorial chemistry, microchips, and assays, to stimulate discovery and development of new therapies for CF. During the past five years, our organization has committed more than $100 million to cutting-edge technologies to aid in the discovery of new compounds for CF. Researchers have now identified several lead compounds that we hope will enter clinical trials in the next 18 months.

We have several suggestions aimed at bringing greater openness, clarity and timeliness to the drug development process. We focus most of our suggestions on ways to improve the development process for drugs and biologics to treat CF, and we believe these advances may have positive benefits for development of treatments for other respiratory, genetic, and orphan diseases. We recommend the agency focus on improving the clinical trial process, identifying and accepting surrogate endpoints, and focusing on approval of drugs to treat life-threatening diseases, such as CF.

Regulatory Improvements

The CF Foundation urges the FDA to provide clear oversight of clinical trials, especially gene therapy trials. **The FDA must take the lead within the Department of Health and Human Services to remove inefficiencies and redundancies in the review process by Institutional Review Boards (IRBs).** Special emphasis should be given to eliminating duplicative IRB review, particularly for multi-center trials, by encouraging centralization or regionalization of IRB review in consultation with the National Institutes of Health (NIH), and with the approval of the Office for Human Research Protections. Although patient safety must be a primary concern in any clinical trial, the current system of review creates duplication and delay without improving patient protections.

We applaud the agency's commitment to the Orphan Product grant program and the resulting increase in orphan drug applications and approved products. However, much more must be done to encourage the development of cures for orphan diseases, particularly as we enter the era of pharmacogenomics, which will parse larger diseases into orphan-like categories. **We encourage the agency to continue to bolster the orphan product grant program for rare diseases such as CF, and to apply the lessons learned there to other FDA programs.**

Clinical Trial Design

The CF Foundation believes the product development process must be revitalized with ingenuity and innovation if we are to cure this disease. To facilitate this, in 1998 we established a network for clinical trials, called the Therapeutics Development Network (TDN), specifically to work with industry to pursue new treatments for CF. The network, which links key CF clinical research centers with a centralized coordinating center, is a critical enticement for industry to focus on CF, as its leaders provide expert advice on trial design and its very structure facilitates patient recruitment. Expanded twice, the network now includes 18 centers across the country. The network also features centralized data management and analysis and a coordinated system of data safety monitoring with disease-specific expertise for protection of patients. Since the launch of the TDN, nearly thirty clinical trials have been completed or are underway. Any of these products in clinical trials could have a major impact on the disease or provide an ultimate cure.

The CF Foundation, with its active research community and Therapeutics Development Network Coordinating Center, champions efficient clinical trial design, and identification of appropriate endpoints for effective trials in CF. Determining proper endpoints is a critical decision in product development. **The FDA must make a concerted effort to meet with development teams to identify and accept more appropriate clinical endpoints.** These endpoints can make all the difference in product development.

We encourage the FDA to meet with the CF Foundation to reach early agreement on trial design and develop consensus on appropriate biomarkers and surrogate endpoints that are most promising for CF, and to replicate this outreach with other nonprofit research organizations. The FDA's acceptance of such endpoints could reduce the risk of failure

in late stage trials by bringing greater certainty to the process sooner, as well as minimizing the number of patients required for trial participation. **The FDA must clearly identify its standards for accepting clinically relevant endpoints that have been recommended by leading researchers, clinicians, and disease advocates.**

In the case of products that may affect the lung functioning of people with CF, FDA should accept results from imaging tests to measure progress toward a trial endpoint. New imaging techniques can help to identify potentially important changes in lung architecture, a leading indicator that the product will positively affect lung function. Imaging is particularly important for pediatric trials where typical measures of improved lung function using pulmonary function tests are not obtainable. If a trial must show improved organ function as the endpoint, drug development could be stymied.

For orphan diseases, the number of patients required for clinical trials make it imperative to perform some trials overseas. **We encourage the FDA to accept more clinical trial data from outside the U.S., including Europe.** Increasing international harmonization on safeguards, processes and data collection for clinical trials is critical for efficient, timely drug approval, particularly for orphan diseases.

New Uses for Old Drugs

We encourage Congress and the FDA to examine ways to encourage investigations into off-label uses of approved medications for rare diseases. The CF Foundation has been successful in demonstrating the benefits of the drug, Azithromycin, in a Phase III trial which enhanced the health of people with CF through improved lung function and weight gain, and reduced hospitalizations compared with placebo. However, these large studies are costly, and companies do not have sufficient incentives to identify new uses for already approved medications for rare diseases. We encourage Congress to provide incentives for off-label uses of drugs for orphan populations, comparable to the incentives in the Best Pharmaceuticals for Children Act or the Orphan Drug Act.

In addition, we are facing greater difficulty achieving rapid accrual to important CF trials, despite the general willingness of CF patients to participate and the efforts of CF clinical centers to educate patients about trials. **We encourage the FDA to undertake steps to educate the public about the essential role of individuals who participate in clinical trials.**

Standardization of Devices

People with CF must use several medical devices to maintain or improve lung health. With the availability of more drugs that must be aerosolized for delivery to the lungs, the development of user-friendly delivery devices for multiple types of drugs and biologics is critical. **We urge the FDA to identify ways to encourage manufacturers to standardize device performance specifications or to create more uniformity in devices for aerosol delivery.** This will enable product development to be undertaken from a patient-centered approach, which is critical for overall patient acceptance and adherence for improved health.

Partnership for Progress

To achieve our goal of curing disease, the CF Foundation regards the FDA as a critical partner in the development process and encourages the agency to work closely with nonprofit research advocacy organizations in developing life-saving products. Just as the "Roadmap for Medical Research" by the NIH will guide basic research, the FDA's commitment to improving the "Critical Path" plan has the potential to influence clinical development for generations.

In summary, the CF Foundation is pleased that the FDA is undertaking a thorough review of its role in the product development process and striving to identify areas for improvement. We believe this examination is essential to bring products to patients more quickly and safely. Our suggested areas for improvement include the following:

- ?? FDA leadership on regulatory oversight and streamlining of IRB review;
- ?? Continued improvement in the orphan product grant effectiveness for rare diseases;
- ?? Identification of processes for the FDA to determine and accept clinical endpoints;
- ?? International harmonization regarding clinical development overseas;
- ?? Incentives for clinical trials for off-label uses of approved medications for rare diseases;
- ?? Education of the public about the importance of clinical trial participation; and
- ?? Standardization of performance specifications for certain medical devices.

Thank you for the opportunity to comment on the FDA's Critical Path to reevaluate agency programs in order to bring life-saving products to patients more rapidly, more efficiently and without compromising patient safety. The CF Foundation looks forward to working closely with the FDA to achieve these goals for people with CF.

Sincerely,

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